Paper No. 39

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte SONIA E. SANHUEZA,
MARY E. EWASYSHYN, and
MICHEL H. KLEIN

Appeal No. 2003-1083
Application No. 08/286,189

ON BRIEF

Before WINTERS, WILLIAM F. SMITH, and MILLS, Administrative Patent Judges.

WILLIAM F. SMITH, Administrative Patent Judge.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 from the final rejection of claims 1, 3 through 9, and 11 through 16, all the claims remaining in the application.

Claims 1, 5, 6, 7, 8, and 9 are representative of the subject matter on appeal and read as follows:

1. A vaccine composition capable of producing a respiratory syncytial (RS) virus specific protective immune response in a human host immunized therewith, comprising a purified, inactivated RS viral preparation which is free from cellular and serum components and which is non-infectious, non-immunopotentiating, immunogenic and protective, and a carrier therefor.

5. A method of preparing a non-immunopotentiating, vaccine composition capable of protecting a human host immunized therewith against disease caused by infection by respiratory syncytial (RS) virus, which comprises:

(a) growing RS virus on a continuous cell line of vaccine quality to produce a grown virus;

(b) harvesting said grown virus to produce a harvested virus;

(c) purifying said harvested virus under non-denaturing conditions to produce a purified virus free from cellular and serum components;

(d) inactivating said purified virus with an inactivating agent to provide a non-infectious, non-immunopotentiating and protective RS viral preparation, and

(e) formulating said non-infectious, non-immunopotentiating and protective RS viral preparation as a vaccine.

6. The method of claim 5 wherein said inactivating agent is β-propiolactone.

7. The method of claim 5 wherein said inactivating agent is a non-ionic detergent.

8. The method of claim 7 wherein said non-ionic detergent is selected from the group consisting of n-octyl-α-D-glucopyranoside and n-octyl-β-D-glucopyranoside.

9. The method of claim 5 wherein said inactivating agent is ascorbic acid.

The references relied upon by the examiner are:

Salkind et al. (Salkind), "Recent Observations Regarding the Pathogenesis of Recurrent Respiratory Syncytial Virus Infections: Implications for Vaccine Development," Vaccine, Vol. 10, No. 8, pp. 519-523 (1992)

Tristam et al. (Tristam), "Respiratory Syncytial Virus Vaccines: Can We Improve on Nature?," Pediatric Annals, Vol. 22, pp. 715-718 (1993)

Hall, "Prospects for a Respiratory Syncytial Virus Vaccine," Science, Vol. 265, pp. 1393-1394 (1994)

Murphy et al. (Murphy), An Update on Approaches to the Development of Respiratory Syncytial Virus (RSV) and Parainfluenza Virus Type 3 (PIV3) Vaccines," Vir. Res., Vol. 32, pp. 13-36 (1994)

Toms, "Respiratory Syncytial Virus -- How Soon Will We Have a Vaccine?," Arch. Dis. Child., Vol. 72, pp. 1-3 (1995)

Claims 1, 3 through 9, and 11 through 16 stand rejected under 35 U.S.C. § 112, first paragraph (enablement). We reverse.

Background

The claimed invention is directed to a method of preparing a vaccine composition capable of protecting a human host immunized therewith against disease cause by infection by respiratory syncytial virus (RSV). Human RSV is stated to be "the main cause of lower respiratory tract infections among infants and young children." Specification, page 1 (reference citations omitted). Appellants state that a safe and effective RSV vaccine is not available but is urgently needed. Id., page 2. Previous attempts to develop a RSV vaccine have included inactivation of the virus with formaldehyde, isolation of cold-adapted and/or temperature-sensitive mutant viruses and isolation of the protective antigens of the virus. Id. None of those approaches resulted in a clinically effective vaccine. Id.

The claims on appeal are directed to RSV vaccine compositions and methods for their preparation. As disclosed in the specification, rather than inactivating a purified virus with formalin as proposed in the prior art, the present invention uses as an inactivating agent a compound selected from the group consisting of β-propiolactone, a

non-ionic detergent which is n-octyl-α-D-glucopyranoside or n-octyl-β-D-glucopyranoside, and ascorbic acid. Specification, page 4, lines 20-36.

Example IX of the specification is stated to illustrate the ability of a RSV preparation inactivated according to the present invention to elicit a protective response in immunized cotton rats without causing enhanced pulmonary pathology. Id., pages 17-19.

Discussion

In making the enablement rejection, the examiner does not dispute that the inactivated RSV preparation used in Example IX of the specification did elicit a protective immune response in the cotton rat without causing the exasperated pulmonary pathology associated with other putative vaccine compositions. Rather, the examiner's position is that "[t]he specification does not provide any data from art-recognized primate models or from preliminary clinical studies." Examiner's Answer, page 4. The examiner then provides a fact-based analysis of the Wands factors.[1]

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[1] In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988):

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman, [230 USPQ 546, 547 (BdPatAppInt 1986)]. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. (footnote omitted).

A key finding made by the examiner is that the cotton rat model used by appellants is purportedly not an art-recognized animal model. Specifically the examiner states:

> The disclosure fails to provide data from an art-recognized animal model. The art teaches that a suitable RSV vaccine animal model that enables the direct extrapolation of results obtained from in vivo studies to the clinic has not been developed (Hall, 1994; Toms, 1995; Murphy et al., 1994). Hall concludes (see p. 1394, middle col., first paragraph) that 'Currently there is no accurate way to predict the response of infants to a candidate vaccine before actual administration.' Murphy and colleagues question the utility of the cotton rat model and note (see pp. 16 and 17, bridging paragraph) that 'the extent of RSV replication in cotton rats is much less than that in humans, and, consequently, the magnitude of immunopathological reactions would be expected to be more limited in scope". The authors also reported (see p. 17, first and second paragraphs) that immunogenic compositions with favorable characteristics in murine systems often fail in primate systems because of reduced immunogenicity, among other factors. Toms also adds (see p. 2, right col., last paragraph) that the 'Protection of animals in the laboratory is much more easily achieved than protection of infants against natural infection.' Thus, the skilled artisan, upon perusal of the art, would reasonably conclude that the cotton rat model does not represent a reasonable system for assessing the efficacy of a putative human RSV vaccine.

Examiner's Answer, paragraph bridging pages 6 and 7.

In making this point, we believe the examiner has overstated his case and/or misapprehended the teachings of the references relied upon. For example, the portion of Murphy relied upon by the examiner reads in its entirety as follows:

> An important advance in RSV vaccine development resulted from the development of an experimental model for RSV disease potentiation in which cotton rats immunized with FI-RSV vaccine developed enhanced pulmonary histopathology during subsequent RSV challenge (Prince et al., 1986). This observation in cotton rats is thought to recapitulate, in an experimental animal, the disease potentiation that was observed in the FI-RSV vaccines in the 1960's. It has since become apparent that the extent

> of RSV replication in cotton rats is much less than that in humans, and, consequently, the magnitude of immunopathological reactions would be expected to be more limited in scope. Despite this limitation, it now became possible to test new vaccines, such as the F subunit vaccine, against FI-RSV for their ability to cause disease potentiation. Evaluated in this way, immunization with purified F glycoprotein produced in mammalian or insect cells was shown to result in enhanced pulmonary histopathology in cotton rats challenged with RSV 3-6 months following immunization. The pattern and magnitude of the cellular infiltration in the lungs of these RSV-challenged animals was similar to that present in FI-RSV immunized, challenged cotton rats (Murphy et al., 1990; Connors et al., 1992a). In addition, FI-RSV and purified F subunit vaccines (as well as purified G or N protein) can induce enhancement of pulmonary histopathology in mice (Vaux-Peretz et al., 1992). It is important to indicate that the interpretation of findings in cotton rats is controversial (see Hildreth et al., 1993a, 1993b; Murphy, 1993). Nevertheless, these findings demonstrated that FI-RSV and subunit F preparations could induce a similar pattern of immunological response in animals that resulted in enhanced pulmonary infiltration with inflammatory cells upon challenge with RSV.

Murphy, paragraph bridging pages 16 and 17.

As seen, Murphy states that the cotton rat model was an important advance in respiratory syncytial virus vaccine development and establishes that the cotton rat model is of value in this field.

Furthermore, the examiner's analysis of the enablement issue in this case does not take into account the correct legal standard. The court stated in In re Brana, 51 F.3d 1560, 1568, 34 USPQ2d 1436, 1442 (Fed. Cir. 1995), their "firm conviction that one who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant and useful contribution to the art, even though it may eventually appear that the compound is without value in the treatment of humans." The court went on to state "[u]sefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily

includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans." Id.

Taking this legal standard into account and understanding that the cotton rat model used in the examples of this application is of value in the art, we do not find that the examiner has established a prima facie case of lack of enablement.

OTHER ISSUE

1. Enablement

As explained, the examiner focused on the cotton rat model in making the extant enablement rejection. In reviewing the case, we find a second enablement issue that does not seem to have been explored by the examiner and appellants. In presenting their respective positions in this appeal, the examiner and appellants have not discussed the merits of the individual claims. We think it important that the examiner review the merits of the claims in an individual manner in view of their disparate scope. Claims 1-5, 11, 15 and 16 require the presence of inactivated RSV but do not specify the inactivating agent. Claims 6, 8, 9 and 12-14 are specific to the inactivating agent used while claim 7 is directed to the class of non-ionic detergents as the inactivating agent.

Appellants acknowledge that the prior art establishes that formalin inactivated RSV vaccines did not work. The present specification sets forth examples that indicate under the applicable legal standards that the four specific inactivating agents of the present invention are enabled. The question arises as to whether a person of skill in

the art would be able to make and use vaccines of the scope of claims 1-5, 7, 11, 15 and 16 without undue experimentation using inactivating agents other than the four specific agents claimed in claims 6, 8 and 9? This question can only be answered by analyzing the prior art and the present disclosure using the legal standards set forth above. Given the complex legal and factual nature of this inquiry and relative lack of discussion concerning the state of the prior art in the record, this analysis is best made by the examiner in the first instance.

In raising this issue, we do not express an opinion one way or the other as to the merits. Only that the record will be clearer if the examiner would discuss why claims such as claim 1 are or are not enabled.

2. Obviousness-type double patenting

Appellants state that the issues in this appeal are related to the issues raised in Application No. 08/583,124, Appeal No. 2003-1079. We have considered the two appeals together. In so doing it is apparent that the claims pending in each case are quite similar. Applicants filed a terminal disclaimer in Application No. 08/583,124 to obviate an obviousness-type double patenting rejection based upon the claims in this case. It does not appear that an obviousness-type double patenting rejection has been made in this application on the basis of the claims in Application No. 08/583,124. Upon return of this application, the examiner should review both sets of claims and determine whether an obviousness-type double patenting should be instituted in this case.

The decision of the examiner is reversed.[2]

REVERSED

Sherman D. Winters)
Administrative Patent Judge)
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William F. Smith) BOARD OF PATENT
Administrative Patent Judge) APPEALS AND
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Demetra J. Mills) INTERFERENCES
Administrative Patent Judge)

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[2] In presenting their case in the Appeal Brief, appellants attached and relied upon a declaration filed under 37 CFR § 1.132 of Professor Gregory A. Prince. In submitting this new evidence, appellants did not make any showing under 37 CFR § 1.195 ("Affidavits, declarations, or exhibits submitted after the case has been appealed will not be admitted without a showing of good and sufficient reasons why they were not earlier presented."). The examiner advised appellants at the time of the Examiner's Answer that the declaration was not entered. See, e.g., Examiner's Answer, page 8. Accordingly, we have not considered the declaration in considering the merits of this appeal.

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